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## The Genetic Landscape of Hematopoietic Stem Cell Frequency in Mice.

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### Public Summary:

We demonstrate the power of the Hybrid Mouse Diversity Panel as a platform to identify the genetic determinants of highly relevant biomedical traits that would otherwise not be feasible or logistically challenging to investigate in humans.

### Scientific Abstract:

Prior efforts to identify regulators of hematopoietic stem cell physiology have relied mainly on candidate gene approaches with genetically modified mice. Here we used a genome-wide association study (GWAS) strategy with the hybrid mouse diversity panel to identify the genetic determinants of hematopoietic stem/progenitor cell (HSPC) frequency. Among 108 strains, we observed approximately 120- to 300-fold variation in three HSPC populations. A GWAS analysis identified several loci that were significantly associated with HSPC frequency, including a locus on chromosome 5 harboring the homeodomain-only protein gene (Hopx). Hopx previously had been implicated in cardiac development but was not known to influence HSPC biology. Analysis of the HSPC pool in Hopx<sup>-/-</sup> mice demonstrated significantly reduced cell frequencies and impaired engraftment in competitive repopulation assays, thus providing functional validation of this positional candidate gene. These results demonstrate the power of GWAS in mice to identify genetic determinants of the hematopoietic system.

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